

## Hypervolemia and blood pressure in prevalent kidney transplant recipients

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## **Title**

Hypervolemia and Blood Pressure in Prevalent Kidney Transplant Recipients

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### **Author's Contributions**

Winnie Chan, Jos A Bosch, David Jones and Richard Borrows participated in research design.

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Phillips and Richard Borrows participated in the writing of the paper. Winnie Chan, Nicholas Inston, Sue Moore, Okdeep Kaur, and Richard Borrows participated in the performance of the research. Winnie Chan, Anna Phillips and Richard Borrows participated in data analysis.

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### **Conflict of Interest**

The authors declare no conflicts of interest.

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## **Abbreviations**

Alpha-Adrenergic Blocker ( <b>AAB</b> )	Haemoglobin ( <b>Hb</b> )
Analysis of Variance ( <b>ANOVA</b> )	High-Sensitivity C-Reactive Protein
Angiotensin-Converting-Enzyme-Inhibitor	( <b>hsCRP</b> )
( <b>ACEI</b> )	Interquartile Range ( <b>IQR</b> )
Angiotensin-Receptor Blocker ( <b>ARB</b> )	Kidney Disease: Improving Global
Albumin ( <b>Alb</b> )	Outcomes ( <b>KDIGO</b> )
Albumin : Creatinine Ratio ( <b>ACR</b> )	Kidney Transplant Recipients ( <b>KTRs</b> )
B-type Natriuretic Peptide ( <b>BNP</b> )	Lean Tissue Index ( <b>LTi</b> )
Blood Pressure ( <b>BP</b> )	Mean Arterial Pressure ( <b>MAP</b> )
Body Composition Monitor ( <b>BCM</b> )	N-terminal Fragment of Prohormone B-type
Calcium Channel Blocker ( <b>CCB</b> )	Natriuretic Peptide ( <b>NT-proBNP</b> )
Chronic Kidney Disease ( <b>CKD</b> )	New Onset Diabetes After Transplantation
Diastolic Blood Pressure ( <b>DBP</b> )	( <b>NODAT</b> )
Dietary Approach to Stop Hypertension	Percentage Volume Expansion ( <b>%VE</b> )
( <b>DASH</b> )	Presence of Diabetes Mellitus Pre-
End Stage Renal Disease ( <b>ESRD</b> )	Transplantation ( <b>Pre-DM</b> )
Estimated Glomerular Filtration Rate ( <b>eGFR</b> )	Prohormone B-type Natriuretic Peptide
European Renal Best Practice ( <b>ERBP</b> )	( <b>Pro-BNP</b> )
Extracellular Fluid ( <b>ECF</b> )	Standard Deviation ( <b>SD</b> )
Fat Tissue Index ( <b>FTI</b> )	Systolic Blood Pressure ( <b>SBP</b> )

## **Abstract**

**Background:** The prevalence and consequences of hypervolemia in kidney transplant recipients (KTRs) have not been investigated. Specifically, its impact on blood pressure (BP) and relationship with N-terminal fragment of prohormone B-type natriuretic peptide (NT-proBNP) are unknown. The objectives of this study were to establish the prevalence of hypervolemia among clinically stable KTRs, investigate the predictors of post-transplant hypervolemia, assess its impact on blood pressure, and determine its relationship with NT-proBNP.

**Methods:** This single-centre cross-sectional study enrolled 123 clinically stable KTRs. Extracellular volume status was determined by multi-frequency bioimpedance analysis. Mild and severe hypervolemia were defined as percentage volume expansion of  $>7\%$  and  $>15\%$  respectively. Systolic BP (SBP) and diastolic BP (DBP) were measured, with mean arterial pressure (MAP) calculated. Serum NT-proBNP was quantified using a non-competitive immunoluminometric assay. Potential demographic, nutritional and clinical predictors of extracellular volume status, BP and NT-proBNP levels were assessed.

**Results:** Hypervolemia was present in 30% of KTRs, with 5% classified as severe hypervolemia. Significant predictors of volume expansion were increased sodium intake, advancing age, and reduced fat mass ( $p<0.01$  for all associations). Hypervolemia was the only independent predictor of elevated MAP, SBP and DBP ( $p<0.001$  for all associations). Raised NT-proBNP levels were independently associated with both hypervolemia ( $p=0.01$ ) and allograft dysfunction ( $p=0.03$ ).

**Conclusions:** Hypervolemia is unexpectedly common among clinically stable KTRs. It is closely associated with elevated BP. The relationship with increased sodium intake signals

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potential therapeutic focus. Further study is warranted to prospectively investigate objective measures of extracellular volume status among KTRs.

## **Introduction**

Hypervolemia (or volume expansion) represents isotonic expansion of the extracellular fluid compartment caused by abnormal retention of water and sodium, manifesting as fluid accumulation and swelling in the extremities or lung tissues. It is common among patients with end-stage renal disease (ESRD) requiring maintenance dialysis<sup>1-4</sup>, and is associated with increased morbidity and mortality<sup>1-3,5</sup>. For many of these patients, kidney transplantation is a preferred option of renal replacement therapy to correct metabolic abnormalities. It is assumed that hypervolemia no longer represents a major problem following transplantation, but no study to date confirms or refutes this.

In addition, hypervolemia is associated with hypertension in patients on haemodialysis<sup>2</sup> and peritoneal dialysis<sup>3</sup>, but this relationship has not been studied in kidney transplant recipients (KTRs) despite this complication arising in 75-90% of these patients<sup>6</sup>.

B-type Natriuretic Peptide (BNP) is a cardiac hormone that is synthesized as an amino acid precursor protein and undergoes intracellular modification to a Prohormone BNP (pro-BNP)<sup>7</sup>. It is secreted predominately from the ventricles in response to increased stretch of the ventricular wall<sup>7</sup>. Upon release into the circulation, pro-BNP is cleaved into the biologically active 32-amino acid C-terminal fragment BNP, and the biologically inactive 76-amino acid N-terminal fragment (NT-proBNP)<sup>7</sup>. NT-proBNP possesses a longer half-life time than the biologically active counterpart, hence delivering a superior reflection of pathophysiological situation leading to raised BNP levels<sup>8</sup>. Due to renal metabolism of NT-proBNP,

concentrations also rise with the progression of chronic kidney disease (CKD)<sup>9</sup>. Recent studies have confirmed that it is a marker of extracellular volume overload rather than cardiac dysfunction *per se* in maintenance dialysis patients<sup>10-13</sup>. However, little research has examined this relationship following transplantation, with the 2 studies conducted to date highlighting the inverse relationship between NT-proBNP and allograft function<sup>14,15</sup>.

The primary objectives of this study were to determine the prevalence and predictors for hypervolemia in a stable kidney transplant cohort, and to assess its association with post-transplant hypertension. Secondly, we sought to explore the utility of serum NT-proBNP as a correlate of hypervolemia and renal dysfunction in this cohort.

## **Results**

### **Population characteristics**

The characteristics of the studied population are shown in **Table 1**. The mean percentage volume expansion (%VE)  $\pm$  standard deviation (SD) for the cohort was  $2.6 \pm 7.7\%$ , ranging from  $-17.0\%$  to  $+25.0\%$ . Based on denoted criteria (described in **Materials and Methods**), the prevalence of hypovolemia in KTRs was 11% (13 patients), normovolemia was 59% (73 patients), mild hypervolemia was 25% (31 patients displaying %VE between 7.1 and 15.0%), and 5% suffered from severe hypervolemia (6 patients displaying %VE  $>15.0\%$ ).



## Factors predicting extracellular volume status

On univariate analysis, increasing values for %VE were associated with the following: higher sodium intake (relationship is shown in **Figure 1**), higher fluid intake, older age, pre-existing diabetes, male gender, the use of either an angiotensin-converting-enzyme-inhibitor (ACEI) or angiotensin-receptor blocker (ARB) (grouped as a single category), and the number of antihypertensive medications. The effect sizes for the univariate analyses are shown in **SDC, Table 1**. In the multivariate analysis, only increased sodium intake (beta coefficient,  $\beta = 1.7$ ; 95% confidence interval, CI = 1.2, 2.4;  $p < 0.001$ ) and advancing age ( $\beta = 1.8$ ; 95% CI = 1.0, 2.6;  $p < 0.001$ ) retained statistical significance. In addition, an association emerged in the multivariate analysis between increased %VE and reduced fat tissue index (FTI) ( $\beta = -1.4$ ; 95% CI = -2.2, -0.5;  $p = 0.002$ ). A 51% of the variation in extracellular volume status (%VE) was explained by these variables ( $R^2$ : 51%; **SDC, Table 1**).

## Extracellular volume status and blood pressure

Increasing volume status (higher %VE) was associated with progressive increases in all measures of blood pressure (BP) (systolic blood pressure, SBP,  $r = 0.83$ ,  $p < 0.001$ ; diastolic blood pressure, DBP,  $r = 0.60$ ,  $p < 0.001$ ; mean arterial pressure, MAP,  $r = 0.78$ ,  $p < 0.001$ ; **Figure 2a**). A significant difference across categories of volume status (“hypovolemia”; “normovolemia”; “mild hypervolemia”; “severe hypervolemia”) was seen, with increased BP at higher degrees of extracellular volume status (**Figure 2b**).

The univariate and adjusted analyses describing the predictors of MAP, SBP and DBP are shown in **SDC, Table 2**; **SDC, Table 3**; and **SDC, Table 4** respectively. The following predictor variables displayed univariate, unadjusted associations with higher values for all measures of BP (MAP, SBP and DBP): increasing %VE, increased sodium intake (associations shown in **Figure 3**), older age, diabetes (either pre-existing diabetes, pre-DM; or new onset diabetes after transplantation, NODAT), the use of either an ACEI or ARB, hypoalbuminaemia, male gender, and number of antihypertensive medications. In addition, higher fluid intake was associated with higher MAP and SBP readings, but not DBP. However, in the adjusted model, the only independent predictor of BP was a higher %VE, with this effect seen for MAP ( $\beta = 6.6$ ; 95% CI = 5.6, 7.6;  $p < 0.001$ ), SBP ( $\beta = 9.8$ ; 95% CI = 8.5, 11.0;  $p < 0.001$ ), and DBP ( $\beta = 4.9$ ; 95% CI = 3.7, 6.2;  $p < 0.001$ ). Of note, a substantial proportion of BP variation could be explained by this single predictor variable (62%, 69% and 35% for MAP, SBP and DBP as shown in **SDC, Table 2**; **SDC, Table 3**; and **SDC, Table 4** respectively).

### **NT-proBNP as a marker of hydration status and allograft function**

Median serum NT-proBNP level in this cohort of KTRs was 291.0 (interquartile range, IQR: 65.0-700.4) pmol/L. NT-proBNP levels demonstrated a positively skewed distribution and underwent logarithmic transformation prior to parametric analysis. On univariate analysis, higher %VE, lower estimated glomerular filtration rate (eGFR), and reduced haemoglobin (Hb) level were associated with higher values for NT-proBNP (**SDC, Table 5**). In the multivariate analysis, increasing %VE (Ratio, R = 1.16; 95% CI = 1.03, 1.29;  $p = 0.01$ ), decreasing eGFR (R = 0.95; 95% CI = 0.90, 0.99;  $p = 0.03$ ), and lower Hb level (R = 0.74; 95% CI = 0.58, 0.96;  $p = 0.02$ ) retained significant associations with NT-proBNP. In addition, the absence of a

dihydropyridine calcium channel blocker (CCB) prescription ( $R = 0.63$ ; 95% CI = 0.45, 0.89;  $p < 0.01$ ) and either current or previous smoking history ( $R = 1.46$ ; 95% CI = 1.04, 2.05;  $p = 0.03$ ) were significant predictors of raised NT-proBNP levels in the multivariate model. The relationships of NT-proBNP with % VE and renal allograft function are demonstrated in **Figure 4a** and **Figure 4b** respectively. A 21% of the variation in NT-proBNP was explained by the variables in the final multivariate model.

## **Discussion**

This is the first study to address in detail the prevalence, predictors, and consequences of hypervolemia in KTRs. Based on the previously established definition of hypervolemia, 30% of KTRs were hypervolemic, of whom 5% suffered from severe hypervolemia. Despite a lower incidence when compared to continuous ambulatory peritoneal dialysis<sup>3</sup> or haemodialysis<sup>16</sup> populations, this degree of hypervolemia was unexpected, and is noteworthy in light of the specific selection of a clinically and biochemically stable kidney transplant cohort for this study. Hypervolemia was associated with increasing sodium intake, highlighting an important target for intervention. Dietary sodium restriction has not been formally examined in KTRs, but has gained attention in other contexts<sup>17</sup>. The daily sodium intake in the current cohort of KTRs was 2725mg (118mmol), lower than previously reported (3588 mg/156mmol per day)<sup>18</sup>, but well above the recommendation of Dietary Approach to Stop Hypertension (DASH) guideline (1500-2300 mg/65-100 mmol per day)<sup>19</sup>. Collectively, these findings suggest that reducing sodium intake in line with the DASH diet should be recommended for KTRs presented with hypervolemia.

A recent study demonstrated a relationship between increased sodium intake and higher BP, although the contribution of extracellular volume status was not evaluated therein<sup>18</sup>. Whilst the results of the current study confirmed a univariate association between sodium intake and BP, this relationship did not hold when the effect of extracellular volume status was taken into account. Indeed, hypervolemia was identified as the only independent risk factor for elevated BP, which has a recognised impact upon long-term patient and graft outcomes<sup>20-22</sup>. Although this relationship between hypervolemia and elevated BP resonates with findings in dialysis patients<sup>2,3,23</sup>, this has not been previously demonstrated in KTRs.

Pertinently, the American Society of Hypertension<sup>24</sup> acknowledges the possible role of volume expansion and potential therapeutic role of diuretics in post-transplant hypertension. Other expert review articles also recognise volume expansion as a potential risk factor, although remain guarded over the use of diuretic therapies<sup>25,26</sup>. In the current study, the prevalence of diuretic usage was only 15%, with furosemide being the only diuretic prescription. No association between furosemide usage and volume status was observed, but this may be a reflection of “confounding by indication”. Furthermore, the median dosage of furosemide in this study cohort was 40mg, a dosage which may be insufficient to target hypervolemia in KTRs with a mean eGFR of 44mL/min<sup>27</sup>. Such confounding may also be responsible for the association between renin-angiotensin system blockers (ACEI and ARB), and volume overload, MAP, SBP and DBP, although these associations did not persist in the adjusted analysis.

In regard to other determinants of extracellular volume status, an inverse association between fat mass and volume status was observed in the current study. This phenomenon has been demonstrated in a non-transplanted population<sup>28</sup>, which now extends to the kidney transplant

population. Interestingly renal dysfunction was not identified as one of the predictors of volume status and blood pressure in this study. However, based on the statistical point estimates, eGFR displayed inverse associations with volume overload, MAP, SBP and DBP, and the absence of statistical significance may reflect the study size and range of renal function encountered in this study, and certainly the current results do not exclude the importance of renal function in this setting.

Based on the findings from this study, a multi-modality approach involving the DASH diet and increased diuretic usage may be beneficial in the treatment of volume overload and hypertension in KTRs. Previous studies have shown that synergistic hypotensive effects were achieved when sodium restriction and diuretics were used in combination<sup>29,30</sup>. In particular, the DASH diet, comprising high fruits, vegetables, whole-grains, and low-fat dairy products; and low fat, refined carbohydrates and sodium, has been shown to substantially lower blood pressure in large, randomised, controlled trials<sup>19,31,32</sup>. It has also been proven to potentiate the benefits of antihypertensive medication treatment<sup>31</sup>. Diuretic therapy should be titrated in accordance with volume status and blood pressure. Crucially, meticulous monitoring of both volume status and blood pressure should be in place to ensure optimal management of hypertension in KTRs. In particular, increasing fluid intake is often promoted particularly in the early period post-transplantation, yet also displayed univariate association with volume overload, MAP and SBP, thereby highlighting the importance of judicious assessment of extracellular volume in these patients. Indeed, the findings from this study suggest that more widespread and accurate evaluation of extracellular volume status may facilitate the clinical management of KTRs, and sets the scene for interventional measures which have shown benefit in a recent haemodialysis-based trial<sup>33</sup>. It is hoped that the findings of this study will highlight the importance of extracellular volume status assessment in the management of hypertension, a

tool yet to be incorporated into international guidelines from Kidney Disease: Improving

Global Outcomes (KDIGO)<sup>34</sup>, European Renal Best Practice (ERBP) Work Group<sup>35</sup> and United Kingdom Renal Association (UKRA)<sup>36</sup>.

The independent association between an objective measure of hypervolemia and raised NT-proBNP level is a novel and noteworthy finding of this study, confirming and extending findings from the non-transplanted populations, predominantly patients undergoing dialysis<sup>10-13</sup>. Additionally, reduced allograft function was independently associated with raised NT-proBNP levels, in keeping with findings from previous studies among KTRs<sup>14,15</sup>, due to a reduced renal clearance of NT-proBNP. Although previous studies have suggested NT-proBNP as a marker of cardiac dysfunction in dialysis patients<sup>37,38</sup>, interpretation of these studies is limited by a lack of concomitant and objective measurement of volume status, and by the variation in NT-proBNP levels depending on the timing of blood sampling relative to dialysis treatment. In fact, the most detailed study in dialysis which employed standardised sampling times, simultaneous echocardiography and bioimpedance-based extracellular fluid volume measurements, showed that NT-proBNP was dependent on volume overload *per se*, rather than the echocardiographic parameters of cardiac dysfunction<sup>10,11</sup>. The single study in KTRs addressing the relationship between echocardiography and NT-proBNP level likewise found no relationship between the two parameters<sup>14</sup>. Whilst cardiac function was not assessed in the current study, the findings from this study certainly support the concept that NT-proBNP levels reflect volume status. However, an important caveat is the high variability in the relationship between NT-proBNP levels and both %VE and eGFR. This suggests that although NT-proBNP may be a marker of volume expansion and renal dysfunction, it cannot yet be considered as an accurate surrogate for either. The utility of serial NT-proBNP measurements cannot be discerned by the current study.

Other factors independently associated with elevated NT-proBNP levels included smoking (current and/or ex- smoker), reduced level of Hb, and the absence of CCB prescription as an antihypertensive agent. Although the mechanisms behind these findings are not fully understood and were not the focus of the present study, these results are in keeping with previous observations in non-transplant cohorts<sup>39-45</sup>, and reflecting the “face validity” of the current findings.

This study has limitations that should be acknowledged. It represents a single-centre experience, and validations of the findings are needed in other cohorts. Also, transplant renal artery stenosis is a potential cause for post-transplant hypertension and volume expansion. However, it was not systematically sought in this study due to an estimated prevalence of only 5-10%<sup>46</sup>, and the lack of detection is unlikely to have confounded the results. The cross-sectional nature of this study is unable to establish the causal relationship between predictor and outcome variables. Long-term longitudinal follow-up and experimental interventions are now required to robustly evaluate the impact of extracellular volume status on relevant end-points in kidney transplantation.

In summary, this is the first study to investigate the prevalence, predictors, consequences, and biochemical markers of hypervolemia in KTRs. It points at potential targets for intervention, thereby expanding future avenues for basic and clinical research.

## **Materials and Methods**

## **Participants and study design**

KTRs beyond 1 year post-transplantation, with stable graft function (<10% increase in serum creatinine over preceding 6 months), were recruited to this cross-sectional study between April 2010 and April 2013. Exclusion criteria included episodes of acute rejection within the last 6 months, evidence of sepsis in the last 6 weeks, known active malignancy or chronic infection, history of thyroid disease or adrenal insufficiency, and contra-indications for use of bio-impedance based body composition assessment (implanted or external electronic devices, metallic implants, amputations, pregnancy, and lactation). Of 133 patients approached, 10 did not participate (mainly due to work commitment). The study was approved by the local research ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

## **Data Collection**

### ***Demographics and clinical parameters***

Age, gender, ethnicity, and time post-transplantation were collected from patients' medical records. Smoking status (never smoked, current and ex- smoker) was collected by questionnaire. The following clinical parameters were retrieved from patients' medical records: 1) presence of diabetes, either pre-transplantation (pre-DM) or new onset diabetes



after transplantation (NODAT), 2) prior acute rejection episodes, 3) immunosuppressive medication usage, either prednisolone, calcineurin inhibitor or adjunctive antiproliferative agent, 4) use of anti-hypertensive medications, either angiotensin-converting-enzyme inhibitor (ACEI), angiotensin-receptor blocker (ARB), beta-adrenergic blocker (BAB), dihydropyridine calcium-channel blocker (CCB), or alpha-adrenergic blocker (AAB), and 5) use of diuretic.

Systolic BP (SBP) and diastolic BP (DBP) were measured semi-recumbent with a fully-automatic upper-arm digital blood-pressure monitor (Spot Vital Signs ® LXi, Welch Allyn). Six readings over an 8-10 minute period were taken, with the first reading ignored, and the mean of the remaining 5 used for analysis. This protocol for BP monitoring has been shown to produce measurements comparable to that derived from the 24-hour ambulatory blood pressure monitor, the “gold standard” for the diagnosis of hypertension<sup>47</sup>. Mean arterial pressure (MAP) was subsequently calculated using the formula  $(2DBP + SBP)/3$ <sup>18</sup>.

### ***Laboratory parameters***

Blood samples were collected for measurement of high-sensitivity C-reactive protein (hsCRP), albumin (Alb), haemoglobin (Hb) and estimated glomerular filtration rate (eGFR) derived using 4-variable modification of diet in renal disease equation<sup>48</sup>. Morning urine was collected for assessment of albumin : creatinine ratio (ACR). Analyses were undertaken in accredited hospital haematology and biochemistry laboratories.

Serum NT-proBNP was measured using a non-competitive immunoluminometric assay as described by Khan and colleagues<sup>49</sup>. This highly specific assay shows no cross-activity with atrial natriuretic peptide, BNP, or C-type natriuretic peptide<sup>49</sup>. The inter- and intra- assay coefficients of variation were 2.3 and 4.8% respectively<sup>49</sup>.

### ***Sodium and fluid intakes***

Sodium and fluid intakes were estimated by a 3-day food diary. A multiple-day food diary provides a good estimate of individual's sodium intake<sup>50</sup>, comparable to that derived from the mean 24-hour urinary sodium excretion<sup>50,51</sup>, and produces a reliable and valid record of fluid intake in free-living humans<sup>52</sup>. Participants were given detailed written instructions on completing an accurate dietary record for a 3-day period, which included one weekend day, within one week prior to attending the research visit. These instructions were accompanied by verbal explanation from the researcher, which included training in portion size estimation and documentation for both dining in and eating out. The dietary records were reviewed by the researcher for accuracy and completeness at the research visit. Data was entered into Dietplan6 P3 (Forestfield Software Ltd) nutrition analysis program by the same researcher, avoiding inter-observer variation. Total daily intakes of fluid, energy, all macro- and micro- nutrients, were calculated by this program. No patients were prescribed sodium-containing oral medication at the time of the study.

### ***Measurement of body composition and hydration status; definition of fluid overload***

Body composition and extracellular volume status were assessed by whole body bio-impedance spectroscopy (“body composition monitor” [BCM]; Fresenius Medical Care, Germany). This device has been used in dialysis patients extensively<sup>5</sup>, and has been validated against reference methods for volume status and body composition<sup>53</sup>. The BCM utilises an algorithm based on a 3-compartment body model to evaluate extracellular and intracellular fluid volumes<sup>28</sup>.

Absolute extracellular volume expansion was determined by calculating the difference between the actual amount of extracellular fluid in the body detected by the BCM and the expected amount of extracellular fluid (ECF) predicted by the BCM under normal physiological (i.e. normovolemia) conditions<sup>5,54</sup>. Percentage volume expansion (% VE) is therefore defined as:  $[(\text{Absolute extracellular volume expansion} \times 100) / \text{Expected ECF volume}]$ . In a normal reference population, the 90<sup>th</sup> and the 10<sup>th</sup> percentiles of % VE is  $\pm 7\%$ <sup>5,55</sup>. Increased mortality in haemodialysis patients is observed when % VE  $> 15\%$ <sup>56,57</sup>. Hence, established definitions (and those used in the current study) are based on % VE,  $< -7.0\%$  representing “hypovolemia”, within  $\pm 7.0\%$  indicating “normovolemia”, between  $7.1\%$  and  $15.0\%$  denoting “mild hypervolemia”, and  $> 15.0\%$  demonstrating “severe hypervolemia”.

Measurements were carried out in a standard manner while the patient was lying supine in a flat and non-conductive bed. The inbuilt physiological body composition model measures whole-body bioimpedance spectroscopy at 50 frequencies (5 to 1000 kHz) via electrodes placed on the wrist (proximal to the transverse) and the ankle (arch on the superior side of the foot) on the same side of the body. Results for % VE, together with Lean Tissue Index (LTI [ $\text{kg}/\text{m}^2$ ]) and Fat Tissue Index (FTI [ $\text{kg}/\text{m}^2$ ]), were displayed after each measurement.

## Statistical analysis

Statistical analyses were performed using STATA. Results were presented as mean  $\pm$  standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Unadjusted univariate relationships were evaluated with Pearson's correlation coefficients, and one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple-group comparisons.

Linear regression analysis was used to determine the associations between predictor variables and the continuously-distributed outcome variables, with logarithmic transformation of non-normally distributed data prior to analysis. The analyses were performed in two stages. Initially, the effect of each variable was examined in a series of univariate regression analyses. Subsequently, the joint effect of variables demonstrating some evidence of association on univariate analysis ( $p < 0.20$ ) was examined in a multivariable regression analysis, using a backwards selection procedure to derive the final model. A type 1 error rate  $\leq 5\%$  ( $p \leq 0.05$ ) was considered significant in the final model.

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## **Table Legends**

### **Table 1.** Population Characteristics

## **Figure Legends**

**Figure 1.** Association between Sodium Intake and Extracellular Volume Status (Percentage Volume Expansion, % VE)

**Figure 2a.** Relationship between Extracellular Volume Status (Percentage Volume Expansion, % VE) and Blood Pressure

**Figure 2b.** Comparisons of Blood Pressure among Kidney Transplant Recipients with Different Extracellular Volume Status

**Figure 3.** Association between Sodium Intake and Blood Pressure

**Figure 4a.** Association between Extracellular Volume Status (Percentage Volume Expansion, % VE) and level of NT-proBNP

**Figure 4b.** Association between Renal Function and level of NT-proBNP

## **Supplemental Digital Content (SDC) Legends**

**SDC, Table 1.** Predictors of Extracellular Volume Status (Percentage Volume Expansion, % VE)

**SDC, Table 2.** Predictors of Mean Arterial Pressure (MAP)

**SDC, Table 3.** Predictors of Systolic Blood Pressure (SBP)

**SDC, Table 4.** Predictors of Diastolic Blood Pressure (DBP)

**SDC, Table 5.** Predictors of N-Terminal of prohormone B-type Natriuretic Peptide (NT-proBNP)

**Table 1. Population Characteristics**

	Characteristics
Sample size	n = 123
Gender (%)	Male = 56      Female = 44
* Ethnicity (%)	Caucasian = 77      Asian = 16 Afro-Caribbean = 5      Others = 2
† Mean age (years)	50 ± 15
‡ Median time post-transplantation (years)	5 (2-11)
§ Smoking status (%)	Non-smoker = 63      Current smoker = 8 Ex-smoker = 29
† Mean extracellular volume status: %VE (%)	2.6 ± 7.7
‡ Median level of NT-proBNP (pmol/L)	291.0 (65.0-700.4)
<b>Blood pressure</b>	
† Mean systolic blood pressure (mmHg)	141 ± 19
† Mean diastolic blood pressure (mmHg)	82 ± 13
† Mean arterial pressure (mmHg)	101 ± 13
<b>Immunosuppressive medication usage</b>	
Calcineurin inhibitor (%)	79
Adjunctive antiproliferative agent (%)	87
Prednisolone (%)	77
<b>Dosage of immunosuppressive medications</b>	
‡ Median dose of Tacrolimus (mg/day)	4.0 (2.5-6.0)
‡ Median dose of Cyclosporin (mg/day)	150 (150-200)
† Mean dose of Mycophenolate Mofetil (mg/day)	987 ± 392
† Mean dose of Azathioprine (mg/day)	77 ± 36
‡ Median dose of Prednisolone (mg/day)	5 (5-5)
<b>Anti-hypertensive medication usage</b>	
ACEI / ARB (%)	43
BAB (%)	21
CCB (%)	48
AAB (%)	39
<b>Diuretic medication usage</b>	
Furosemide, exclusively (%)	15
‡ Median dosage of Furosemide (mg)	40 (30-40)
Presence of diabetes (%)	Non-diabetic = 75      NODAT = 15 Pre-DM = 10
Previous episodes of acute rejection (%)	Yes = 23      No = 77
‡ Median hsCRP (mg/L)	2.4 (1.0-4.9)
† Mean Hb (g/dL)	12.6 ± 1.6
† Mean Alb (g/L)	44.5 ± 3.2
† Mean eGFR (mL/min)	44.2 ± 17.3
‡ Median ACR (mg/mmol)	4.4 (1.6-14.7)
‡ Median sodium intake (mg)	2725 (2131-3248)
‡ Median fluid intake (mL)	2567 (2100-3672)
<b>Body Composition</b>	
Body mass index, BMI (kg/m <sup>2</sup> )	27.4 ± 5.8
Lean Tissue Index, LTI (kg/m <sup>2</sup> )	13.9 ± 3.0
Fat Tissue Index, FTI (kg/m <sup>2</sup> )	13.3 ± 6.3

\*For the purpose of statistical analysis, the ethnicity of patients classified as "Afro-Caribbean", "Asian" and "Others" was grouped as "Non-Caucasian", 77% "Caucasian" versus 23% "Non-Caucasian".

†Normally distributed data, results expressed as mean ± standard deviation (SD).

‡Non-normally distributed data, results expressed as median (interquartile range, IQR).

§For the purpose of statistical analysis, smoking status was arranged into 2 categories, "non-smoker" versus "current smoker and ex-smoker", 63% and 37% of patients respectively.

Abbreviations: %VE=Percentage Volume Expansion; NT-proBNP=N-Terminal pro B-type Natriuretic Peptide; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Beta-Adrenergic Blocker; CCB=Calcium Channel Blocker; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein; Hb=Haemoglobin; Alb=Albumin; eGFR=estimated Glomerular Filtration Rate; ACR=Albumin : Creatinine Ratio; BMI=Body Mass Index; LTI=Lean Tissue Index; FTI=Fat Tissue Index; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation.

**SDC, Table 1. Predictors of Extracellular Volume Status (Percentage Volume Expansion, % VE)**

	Univariate Analysis		Multivariate Analysis <sup>§</sup>	
	Regression Coefficient (95% CI <sup>†</sup> )	p-value	Regression Coefficient (95% CI <sup>†</sup> )	p-value
(***) Sodium intake (mg)	1.8 (1.3, 2.3)	<0.001	1.7 (1.2, 2.4)	<0.001
(***) Fluid intake (mL)	1.4 (0.6, 2.0)	<0.001		
(**) Age (years)	1.9 (0.9, 2.8)	<0.001	1.8 (1.0, 2.6)	<0.001
<b>Presence of diabetes</b>				
Non-diabetic	0	<0.001		
NODAT	2.4 (-1.2, 5.9)			
Pre-DM	10.3 (6.0, 14.7)			
<b>Gender</b>				
Female	0	0.002		
Male	4.3 (1.6, 7.0)			
<b>Use of ACEI / ARB</b>				
No	0	0.01		
Yes	3.6 (0.9, 6.3)			
Number of antihypertensive medications	1.6 (0.1, 3.2)	0.04		
Alb (g/L)	-0.4 (-0.8, 0.1)	0.11		
<b>Use of diuretic (furosemide)</b>				
No	0	0.11		
Yes	3.5 (-0.8, 7.8)			
( <sup>§</sup> ) FTI (kg/m <sup>2</sup> )	-1.0 (-2.0, 0.5)	0.12	-1.4 (-2.2, -0.5)	0.002
( <sup>§</sup> ) eGFR (mL/min)	-0.3 (-0.6, 0.1)	0.19		
( <sup>†</sup> ) ACR (mg/mmol)	0.5 (-0.4, 1.4)	0.27		
<b>*Ethnicity</b>				
Caucasian	0	0.29		
Non-Caucasian	-1.8 (-5.1, 1.5)			
<b>Use of prednisolone</b>				
No	0	0.29		
Yes	-1.8 (-5.1, 1.6)			
( <sup>§</sup> ) LTI (kg/m <sup>2</sup> )	-0.2 (-0.7, 0.2)	0.31		
<b>†Smoking status</b>				
Never smoked	0	0.32		
Ex-smoker / Current smoker	0.1 (-1.4, 4.3)			
<b>Use of BAB</b>				
No	0	0.34		
Yes	0.2 (-1.3, 3.9)			
<b>Use of CCB</b>				
No	0	0.34		
Yes	0.1 (-1.5, 4.1)			
Hb (g/dL)	-0.4 (-1.3, 0.5)	0.44		
<b>Use of AAB</b>				
No	0	0.52		
Yes	0.1 (-2.0, 3.9)			
( <sup>§</sup> ) Time post transplantation (years)	0.2 (-0.9, 1.3)	0.76		
<b>Use of calcineurin inhibitor</b>				
No	0	0.85		
Yes	-0.3 (-3.7, 3.1)			
( <sup>†</sup> ) hsCRP (mg/L)	0.1 (-1.3, 1.4)	0.94		
<b>Previous episodes of acute rejection</b>				
No	0	0.95		
Yes	-0.1 (-3.4, 3.2)			
<b>Use of adjunctive antiproliferative agents</b>				
No	0	0.99		
Yes	-0.0 (-4.6, 4.5)			
<b>R<sup>2</sup> value from final model</b>			<b>51%</b>	

<sup>§</sup>Results in the final multivariate regression model were presented.

<sup>†</sup>CI = Confidence Interval.

<sup>†</sup>For the purpose of statistical analysis, smoking status was arranged into 2 categories, “non-smoker” versus “the combination of current smoker and ex-smoker”, 63% and 37% of patients respectively.

<sup>†</sup>For the purpose of statistical analysis, the ethnicity of patients classified as “Afro-Caribbean”, “Asian” and “Others” was grouped as “Non-Caucasian”, 77% “Caucasian” versus 23% “Non-Caucasian”.

(<sup>§</sup>) Coefficients reported for a 5-unit increase in explanatory variable.

(\*\*\*) Coefficients reported for a 10-unit increase in explanatory variable.

(\*\*\*\*) Coefficients reported for a 50-unit increase in explanatory variable.

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<sup>(†)</sup> Variable analysed on the log scale (base 10).

Abbreviations: %VE=Percentage Volume Expansion; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; FTI=Fat Tissue Index; eGFR=estimated Glomerular Filtration Rate; ACR=Albumin : Creatinine Ratio; LTI= Lean Tissue Index; BAB=Beta-Adrenergic Blocker; CCB=Calcium Channel Blocker; Hb=Haemoglobin; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein.

**SDC, Table 2. Predictors of Mean Arterial Pressure (MAP)**

	Univariate Analysis		Multivariate Analysis <sup>§</sup>	
	Regression Coefficient (95% CI <sup>¶</sup> )	p-value	Regression Coefficient (95% CI <sup>¶</sup> )	p-value
<sup>(*)</sup> %VE	6.6 (5.6, 7.5)	<0.001	6.6 (5.6, 7.6)	<0.001
<sup>(***)</sup> Sodium intake (mg)	0.3 (0.2, 0.4)	<0.001		
<sup>(**)</sup> Age (years)	2.5 (0.9, 4.1)	<0.01		
<b>Presence of diabetes</b>				
Non-diabetic	0	<0.01		
NODAT	5.6 (2.1, 9.0)			
Pre-DM	11.2 (2.8, 19.5)			
<b>Use of ACEI / ARB</b>				
No	0	<0.01		
Yes	6.7 (2.1, 11.3)			
Alb (g/L)	-0.9 (-1.7, -0.2)	0.01		
<b>Gender</b>				
Female	0	0.02		
Male	5.8 (1.1, 10.4)			
<sup>(***)</sup> Fluid intake (mL)	0.2 (0.0, 0.3)	0.03		
Number of antihypertensive medications	2.7 (0.0, 5.4)	0.05		
<b><sup>‡</sup>Ethnicity</b>				
Caucasian	0	0.08		
Non-Caucasian	5.0 (-0.5, 11.0)			
<sup>(*)</sup> Time post transplantation (years)	1.2 (-0.6, 2.9)	0.18		
<sup>(*)</sup> FTI (kg/m <sup>2</sup> )	1.3 (-3.1, 0.6)	0.19		
<b>Use of calcineurin inhibitor</b>				
No	0	0.22		
Yes	3.6 (-2.2, 9.3)			
<b>Use of diuretic (furosemide)</b>				
No	0	0.23		
Yes	4.0 (-2.5, 10.5)			
<b>Use of prednisolone</b>				
No	0	0.38		
Yes	-2.5 (-8.1, 3.1)			
<b>Use of CCB</b>				
No	0	0.39		
Yes	2.1 (-2.7, 6.8)			
<b>Use of BAB</b>				
No	0	0.41		
Yes	3.2 (-2.9, 6.2)			
<sup>(*)</sup> eGFR (mL/min)	-0.2 (-0.9, 0.5)	0.54		
Hb (g/dL)	-0.5 (-2.0, 1.1)	0.56		
<b>Use of adjunctive antiproliferative agents</b>				
No	0	0.56		
Yes	2.2 (-5.3, 9.7)			
<b>Use of AAB</b>				
No	0	0.56		
Yes	1.5 (-3.5, 6.5)			
<b><sup>†</sup>Smoking status</b>				
Never smoked	0	0.57		
Ex-smoker / Current smoker	1.4 (-3.5, 6.3)			
LTI (kg/m <sup>2</sup> )	-0.2 (-1.0, 0.6)	0.63		
<sup>(†)</sup> hsCRP (mg/L)	1.1 (-3.8, 5.9)	0.66		
<sup>(†)</sup> ACR (mg/mmol)	0.6 (-3.0, 4.3)	0.72		
<b>Previous episodes of acute rejection</b>				
No	0	0.86		
Yes	-0.5 (-6.1, 5.1)			
<b>R<sup>2</sup> value from final model</b>			<b>62%</b>	

<sup>§</sup> Results in the final multivariate regression model were presented.

<sup>¶</sup> CI = Confidence Interval.

<sup>†</sup> For the purpose of statistical analysis, smoking status was arranged into 2 categories, “non-smoker” versus “the combination of current smoker and ex-smoker”, 63% and 37% of patients respectively.

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<sup>‡</sup>For the purpose of statistical analysis, the ethnicity of patients classified as “Afro-Caribbean”, “Asian” and “Others” was grouped as “Non-Caucasian”, 77% “Caucasian” versus 23% “Non-Caucasian”.

(\*) Coefficients reported for a 5-unit increase in explanatory variable.

(\*\*) Coefficients reported for a 10-unit increase in explanatory variable.

(\*\*\*) Coefficients reported for a 50-unit increase in explanatory variable.

(<sup>†</sup>) Variable analysed on the log scale (base 10).

Abbreviations: %VE=Percentage Volume Expansion; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; FTI=Fat Tissue Index; CCB=Calcium Channel Blocker; BAB=Beta-Adrenergic Blocker; eGFR=estimated Glomerular Filtration Rate; Hb=Haemoglobin; AAB=Alpha-Adrenergic Blocker; LTI= Lean Tissue Index; hsCRP=high-sensitivity C-Reactive Protein; ACR=Albumin : Creatinine Ratio.

### SDC, Table 3. Predictors of Systolic Blood Pressure (SBP)

	Univariate Analysis		Multivariate Analysis <sup>§</sup>	
	Regression Coefficient (95% CI <sup>∞</sup> )	p-value	Regression Coefficient (95% CI <sup>∞</sup> )	p-value
(***) Sodium intake (mg)	0.4 (0.3, 0.6)	<0.001		
(***) Fluid intake (mL)	0.2 (0.1, 0.4)	<0.001		
(**) Age (years)	4.2 (2.0, 6.3)	<0.001		
(*) %VE	9.7 (8.4, 11.0)	<0.001	9.8 (8.5, 11.0)	<0.001
<b>Presence of diabetes</b>				
Non-diabetic	0	<0.001		
NODAT	9.2 (4.3, 14.0)			
Pre-DM	23.9 (12.7, 35.0)			
<b>Use of ACEI / ARB</b>				
No	0	<0.01		
Yes	9.3 (2.8, 15.8)			
<b>Gender</b>				
Female	0	0.02		
Male	8.1 (1.5, 14.6)			
Alb (g/L)	-1.1 (-2.2, -0.1)	0.03		
Number of antihypertensive medications	3.3 (-0.5, 7.0)	0.09		
<b>*Ethnicity</b>				
Caucasian	0	0.20		
Non-Caucasian	5.2 (2.7, 13.1)			
(*) FTI (kg/m <sup>2</sup> )	-1.6 (-4.2, 1.1)	0.24		
( <sup>†</sup> ) ACR (mg/mmol)	2.9 (-2.1, 8.0)	0.25		
<b>Use of diuretic (furosemide)</b>				
No	0	0.28		
Yes	-4.4 (-12.3, 3.5)			
<b>Use of prednisolone</b>				
No	0	0.28		
Yes	-4.4 (-12.3, 3.5)			
LTI (kg/m <sup>2</sup> )	-0.6 (-1.8, 0.5)	0.28		
(*) Time post transplantation (years)	1.2 (-1.2, 3.7)	0.31		
Hb (g/dL)	-0.9 (-3.1, 1.3)	0.42		
<b>Use of calcineurin inhibitor</b>				
No	0	0.53		
Yes	2.6 (-5.6, 10.7)			
<b>Use of BAB</b>				
No	0	0.55		
Yes	-2.1 (-4.4, 7.2)			
<b>Previous episodes of acute rejection</b>				
No	0	0.56		
Yes	-2.4 (-10.3, 5.6)			
<b>Use of CCB</b>				
No	0	0.62		
Yes	1.7 (-5.0, 8.4)			
<b>†Smoking status</b>				
Never smoked	0	0.69		
Ex-smoker / Current smoker	1.4 (-5.5, 8.3)			
(*) eGFR (mL/min)	-0.2 (-1.2, 0.8)	0.71		
<b>Use of AAB</b>				
No	0	0.74		
Yes	1.2 (-5.9, 8.3)			
( <sup>†</sup> ) hsCRP (mg/L)	0.9 (-6.0, 7.8)	0.80		
<b>Use of adjunctive antiproliferative agents</b>				
No	0	0.95		
Yes	0.4 (-10.2, 11.0)			

<b>R<sup>2</sup> value from final model</b>	69%
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<sup>§</sup>Results in the final multivariate regression model were presented.

<sup>°</sup>CI = Confidence Interval.

<sup>†</sup>For the purpose of statistical analysis, smoking status was arranged into 2 categories, “non-smoker” versus “the combination of current smoker and ex-smoker”, 63% and 37% of patients respectively.

<sup>‡</sup>For the purpose of statistical analysis, the ethnicity of patients classified as “Afro-Caribbean”, “Asian” and “Others” was grouped as “Non-Caucasian”, 77% “Caucasian” versus 23% “Non-Caucasian”.

(\*) Coefficients reported for a 5-unit increase in explanatory variable.

(\*\*) Coefficients reported for a 10-unit increase in explanatory variable.

(\*\*\*) Coefficients reported for a 50-unit increase in explanatory variable.

(<sup>†</sup>) Variable analysed on the log scale (base 10).

Abbreviations: %VE=Percentage Volume Expansion; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; FTI=Fat Tissue Index; ACR=Albumin : Creatinine Ratio; LTI= Lean Tissue Index; Hb=Haemoglobin; BAB=Beta-Adrenergic Blocker; CCB=Calcium Channel Blocker; eGFR=estimated Glomerular Filtration Rate; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein.

**SDC, Table 4. Predictors of Diastolic Blood Pressure (DBP)**

	Univariate Analysis		Multivariate Analysis <sup>§</sup>	
	Regression Coefficient (95% CI <sup>°</sup> )	p-value	Regression Coefficient (95% CI <sup>°</sup> )	p-value
(*) %VE	5.0 (3.7, 6.2)	<0.001	4.9 (3.7, 6.2)	<0.001
(***) Sodium intake (mg)	0.2 (0.1, 0.3)	<0.01		
<b>Use of ACEI / ARB</b>				
No	0	0.02		
Yes	5.3 (0.7, 9.9)			
Alb (g/L)	-0.8 (-1.5, -0.1)	0.03		
(**) Age (years)	1.7 (0.1, 3.3)	0.04		
<b>Presence of diabetes</b>				
Non-diabetic	0	0.04		
NODAT	3.7 (0.2, 7.2)			
Pre-DM	4.9 (-3.6, 13.4)			
<b>Gender</b>				
Female	0	0.05		
Male	4.7 (0.0, 9.3)			
<sup>‡</sup> <b>Ethnicity</b>				
Caucasian	0	0.08		
Non-Caucasian	4.9 (-0.6, 10.4)			
Number of antihypertensive medications	2.4 (-0.3, 5.0)	0.08		
(***) Fluid intake (mL)	0.1 (-0.1, 0.2)	0.16		
<b>Use of BAB</b>				
No	0	0.16		
Yes	2.8 (-3.1, 4.8)			
<b>Use of calcineurin inhibitor</b>				
No	0	0.16		
Yes	4.0 (-1.7, 9.6)			
(*) Time post transplantation (years)	1.1 (-0.6, 5.6)	0.21		
<sup>‡</sup> <b>Smoking status</b>				
Never smoked	0	0.23		
Ex-smoker / Current smoker	2.9 (-1.9, 7.7)			
(*) FTI (kg/m <sup>2</sup> )	-1.1 (-3.0, 0.7)	0.24		
<b>Use of CCB</b>				
No	0	0.34		
Yes	2.3 (-2.4, 7.0)			
<b>Use of adjunctive antiproliferative agents</b>				
No	0	0.39		
Yes	3.2 (-4.1, 10.6)			
(*) eGFR (mL/min)	-0.2 (-0.9, 0.5)	0.50		
<b>Use of AAB</b>				
No	0	0.53		
Yes	1.6 (-3.3, 6.5)			
<b>Use of diuretic (furosemide)</b>				
No	0	0.58		
Yes	1.8 (-4.6, 8.2)			
<b>Use of prednisolone</b>				
No	0	0.59		
Yes	-1.5 (-7.1, 4.0)			
( <sup>†</sup> ) hsCRP (mg/L)	1.2 (-3.6, 6.0)	0.62		
( <sup>†</sup> ) ACR (mg/mmol)	-0.6 (-4.1, 3.0)	0.75		
Hb (g/dL)	-0.2 (-1.7, 1.3)	0.77		

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. <http://dx.doi.org/10.1097/TP.0000000000000066>

<b>Previous episodes of acute rejection</b>				
No	0	0.87		
Yes	0.4 (-5.1, 6.0)			
LTI (kg/m <sup>2</sup> )	0.0 (-0.8, 0.8)	0.91		
<b>R<sup>2</sup> value from final model</b>			35%	

<sup>§</sup>Results in the final multivariate regression model were presented.

<sup>°</sup>CI = Confidence Interval.

<sup>†</sup>For the purpose of statistical analysis, smoking status was arranged into 2 categories, “non-smoker” versus “the combination of current smoker and ex-smoker”, 63% and 37% of patients respectively.

<sup>‡</sup>For the purpose of statistical analysis, the ethnicity of patients classified as “Afro-Caribbean”, “Asian” and “Others” was grouped as “Non-Caucasian”, 77% “Caucasian” versus 23% “Non-Caucasian”.

<sup>(\*)</sup> Coefficients reported for a 5-unit increase in explanatory variable.

<sup>(\*\*)</sup> Coefficients reported for a 10-unit increase in explanatory variable.

<sup>(\*\*\*)</sup> Coefficients reported for a 50-unit increase in explanatory variable.

<sup>(†)</sup> Variable analysed on the log scale (base 10).

Abbreviations: %VE=Percentage Volume Expansion; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; Alb=Albumin; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; BAB=Beta-Adrenergic Blocker; FTI=Fat Tissue Index; CCB=Calcium Channel Blocker; eGFR=estimated Glomerular Filtration Rate; AAB=Alpha-Adrenergic Blocker; hsCRP=high-sensitivity C-Reactive Protein; ACR=Albumin : Creatinine Ratio; Hb=Haemoglobin; LTI= Lean Tissue Index.

**SDC, Table 5. Predictors of N-Terminal of prohormone B-type Natriuretic Peptide (NT-proBNP)**

	Univariate Analysis		Multivariate Analysis <sup>§</sup>	
	Ratio (95% CI <sup>°</sup> )	p-value	Ratio (95% CI <sup>°</sup> )	p-value
<sup>(*)</sup> % VE	1.38 (1.07, 1.78)	0.01	1.16 (1.03, 1.29)	0.01
<sup>(*)</sup> eGFR (mL/min)	0.89 (0.80, 0.99)	0.03	0.95 (0.90, 0.99)	0.03
Hb (g/dL)	0.74 (0.57, 0.96)	0.03	0.74 (0.58, 0.96)	0.02
<b>Use of CCB</b>				
No	1	0.09	1	<0.01
Yes	0.84 (0.53, 1.05)		0.63 (0.45, 0.89)	
<sup>(†)</sup> ACR (mg/mmol)	1.24 (0.96, 1.60)	0.10		
<b>Use of adjunctive antiproliferative agents</b>				
No	1	0.11		
Yes	0.85 (0.40, 1.10)			
<b>†Smoking status</b>				
Never smoked	1	0.12	1	0.03
Ex-smoker / Current smoker	1.16 (0.93, 1.84)		1.46 (1.04, 2.05)	
LTI (kg/m <sup>2</sup> )	0.96 (0.91, 1.02)	0.20		
<sup>(**)</sup> Age (years)	1.20 (0.91, 1.59)	0.20		
<sup>(*)</sup> Time post transplantation (years)	1.20 (0.91, 1.60)	0.20		
<b>‡Ethnicity</b>				
Caucasian	1	0.21		
Non-Caucasian	0.56 (0.23, 1.40)			
<b>Use of prednisolone</b>				
No	1	0.29		
Yes	0.17 (0.01, 4.75)			
<sup>(†)</sup> hsCRP (mg/L)	0.83 (0.58, 1.19)	0.31		
<b>Gender</b>				
Female	1	0.33		
Male	0.68 (0.32, 1.47)			
<b>Use of AAB</b>				
No	1	0.41		
Yes	1.09 (0.82, 1.64)			
<b>Presence of diabetes</b>				
Non-diabetic	1	0.42		
NODAT	2.02 (0.69, 5.96)			
Pre-DM	1.32 (0.37, 4.70)			
<b>Use of BAB</b>				
No	1	0.45		
Yes	0.98 (0.81, 1.28)			
<b>Use of calcineurin inhibitor</b>				
No	1	0.48		
Yes	1.44 (0.52, 4.01)			
<sup>(***)</sup> Fluid intake (mL)	1.07 (0.86, 1.33)	0.53		
Number of antihypertensive medications	0.95 (0.79, 1.16)	0.63		
Alb (g/L)	1.03 (0.91, 1.17)	0.67		
<b>Use of diuretic (furosemide)</b>				
No	1	0.81		
Yes	1.02 (0.67, 1.67)			

Post-print cite as: Chan, W., Jones, D., Bosch, J.A., McTernan, P.G., Inston, N., Moore, S., Kaur, O., Phillips, A.C. & Borrows, R. (2014). Hypervolemia and blood pressure in prevalent kidney transplant recipients. *Transplantation*, 98, 320–327. <http://dx.doi.org/10.1097/TP.0000000000000066>

<b>Use of ACEI / ARB</b>				
No	1	0.90		
Yes	1.05 (0.48, 2.28)			
<sup>(*)</sup> FTI (kg/m <sup>2</sup> )	1.01 (0.88, 1.15)	0.95		
<sup>(***)</sup> Sodium intake (mg)	1.01 (0.84, 1.20)	0.95		
<b>Previous episodes of acute rejection</b>				
No	1	0.98		
Yes	1.01 (0.36, 2.89)			
<b>R<sup>2</sup> value from final model</b>			<b>21%</b>	

<sup>§</sup>Results in the final multivariate regression model were presented.

<sup>°</sup>CI = Confidence Interval.

<sup>†</sup>For the purpose of statistical analysis, smoking status was arranged into 2 categories, “non-smoker” versus “the combination of current smoker and ex-smoker”, 63% and 37% of patients respectively.

<sup>‡</sup>For the purpose of statistical analysis, the ethnicity of patients classified as “Afro-Caribbean”, “Asian” and “Others” was grouped as “Non-Caucasian”, 77% “Caucasian” versus 23% “Non-Caucasian”.

<sup>(\*)</sup> Coefficients reported for a 5-unit increase in explanatory variable.

<sup>(\*\*)</sup> Coefficients reported for a 10-unit increase in explanatory variable.

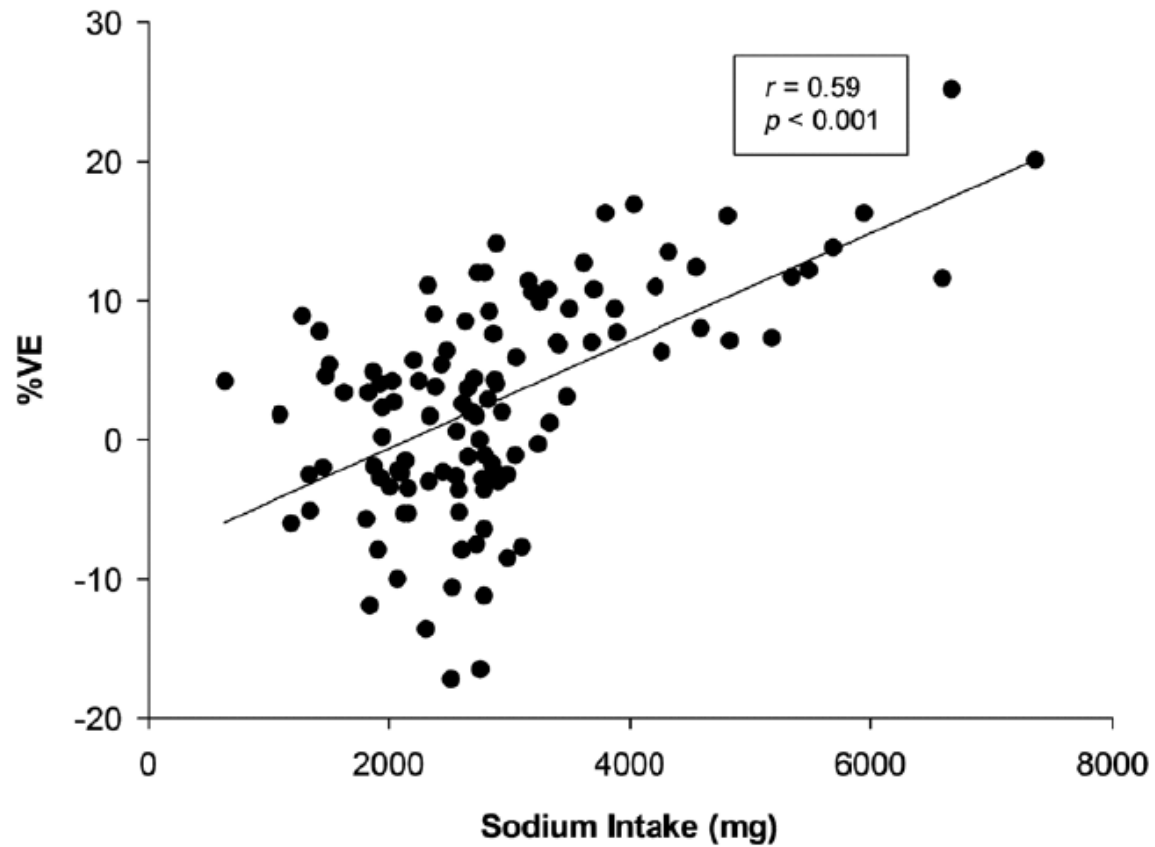
<sup>(\*\*\*)</sup> Coefficients reported for a 50-unit increase in explanatory variable.

<sup>(†)</sup> Variable analysed on the log scale (base 10).

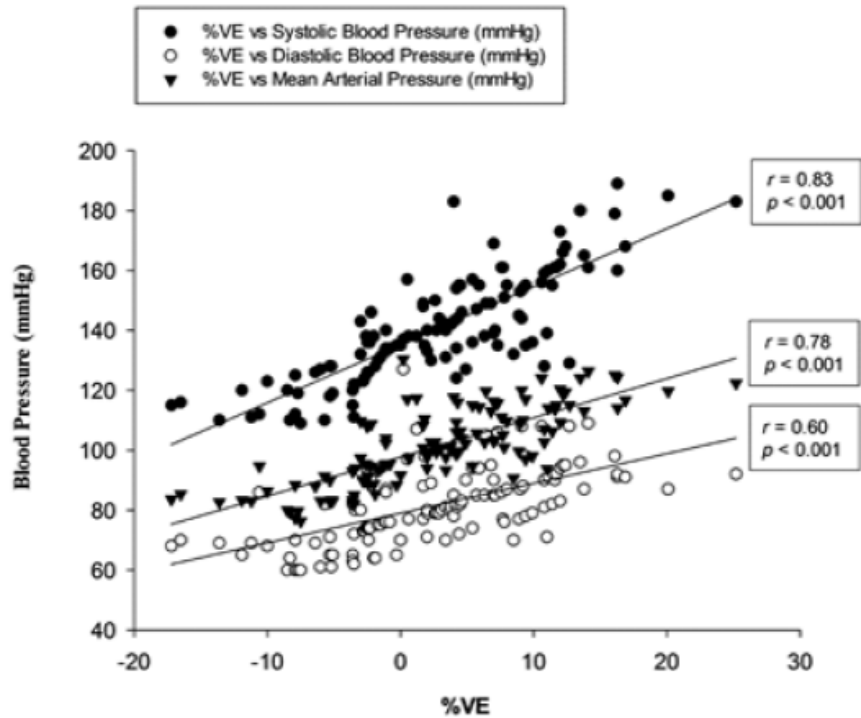
Abbreviations: NT-proBNP=N-Terminal pro B-type Natriuretic Peptide; %VE=Percentage Volume Expansion; eGFR=estimated Glomerular Filtration Rate; Hb=Haemoglobin; CCB=Calcium Channel Blocker; ACR=Albumin : Creatinine Ratio; LTI= Lean Tissue Index; hsCRP=high-sensitivity C-Reactive Protein; AAB=Alpha-Adrenergic Blocker; NODAT=New Onset Diabetes After Transplantation; Pre-DM=Presence of Diabetes Mellitus pre-transplantation; BAB=Beta-Adrenergic Blocker; Alb=Albumin; ACEI=Angiotensin-Converting-Enzyme Inhibitor; ARB=Angiotensin-Receptor Blocker; FTI=Fat Tissue Index.



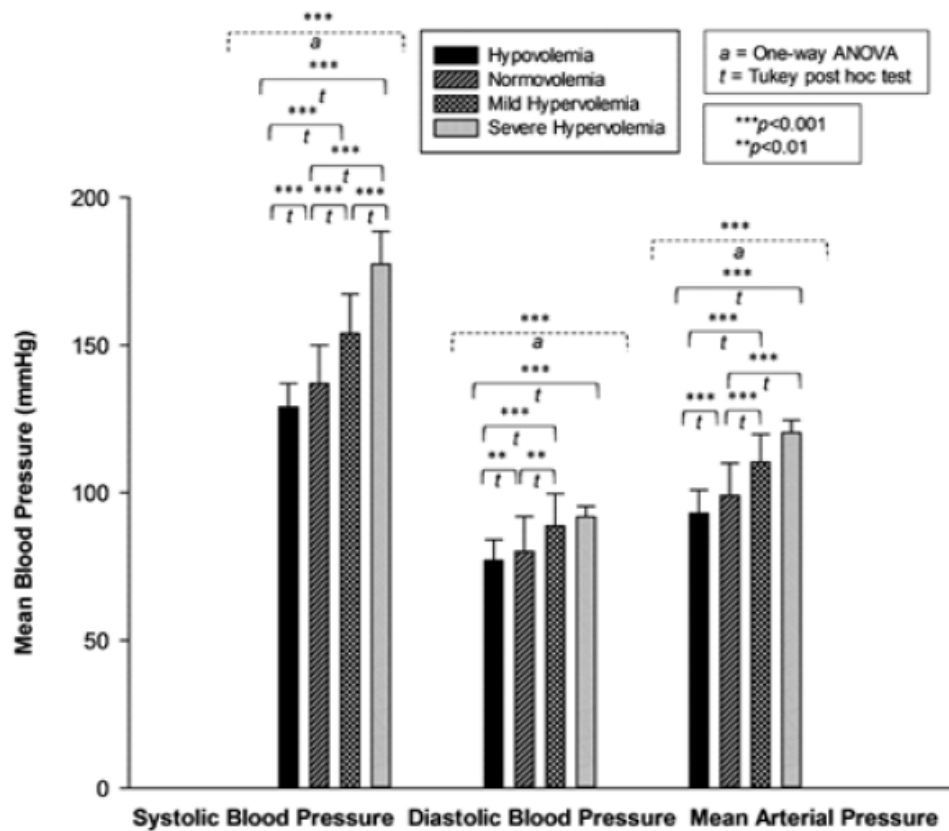
**Figure 1. Association between Sodium Intake and Extracellular Volume :  
(Percentage Volume Expansion, %VE)**



**Figure 2a. Relationship between Extracellular Volume Status (Percentage Volume Expansion, %VE) and Blood Pressure**

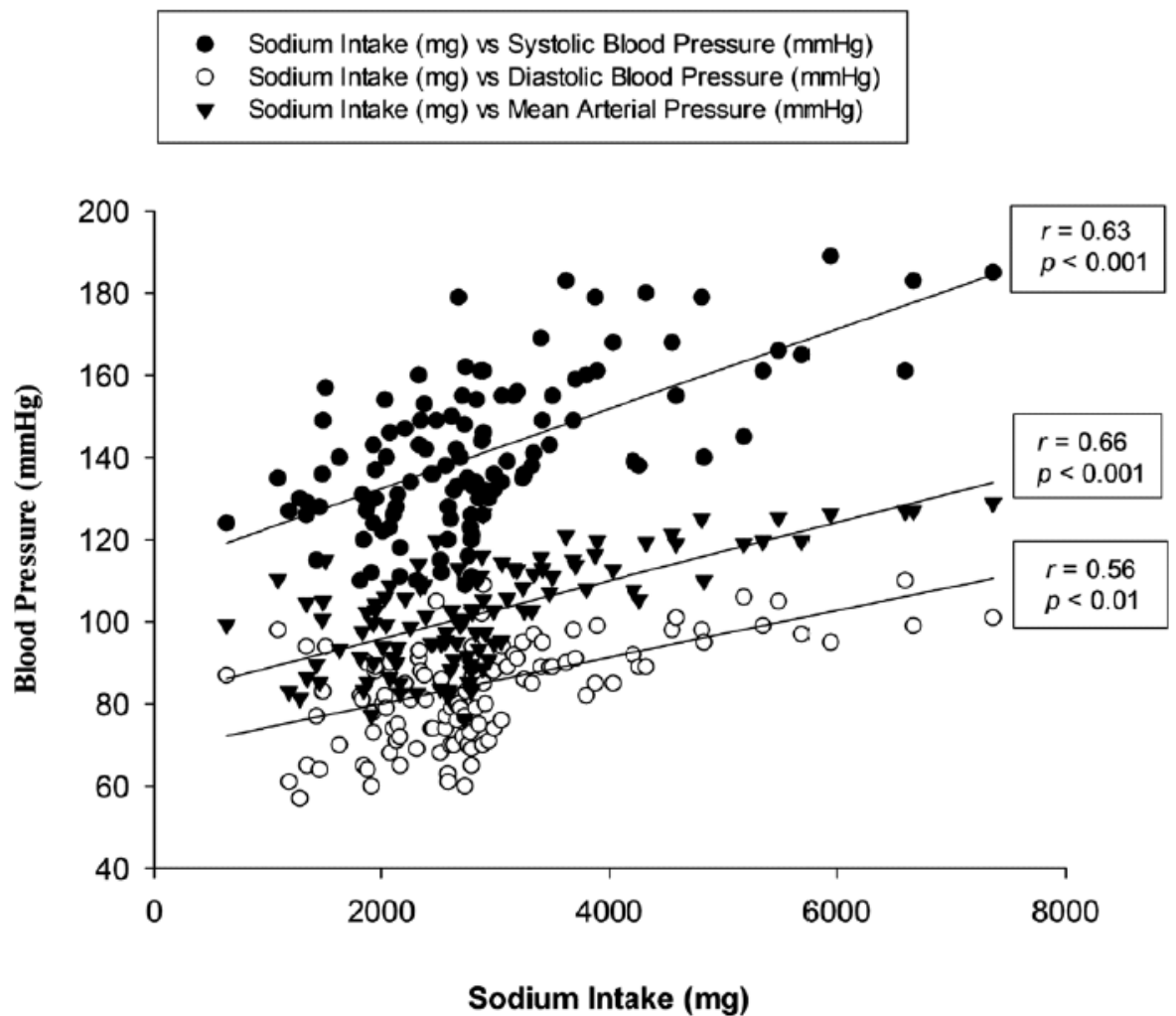


**Figure 2b. Comparisons of Blood Pressure among Kidney Transplant Recipients with Different Extracellular Volume Status**

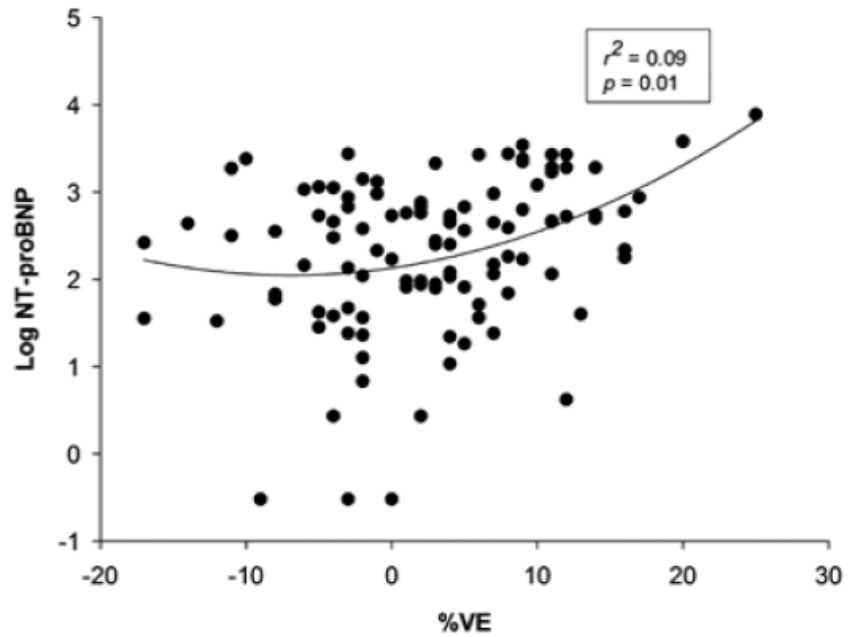


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**Figure 3. Association between Sodium Intake and Blood Pressure**



**Figure 4a. Association between Extracellular Volume Status (Percentage Volume Expansion, %VE) and level of NT-proBNP**



**Figure 4b. Association between Renal Function and level of NT-proBNP**

